PROJECT PROPOSAL

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This year prostate cancer has surpassed lung cancer as the most commonly diagnosed cancer in U.S. males and is the second leading cause of cancer deaths in men. The occurrence of prostate cancer in the adult is thought to require the presence of androgens at an early stage of life. The mechanism(s) by which androgens regulate prostate cells is poorly understood. A few androgen-regulated genes have been described in human prostate. One of these, prostate-specific antigen (PSA), is a very sensitive indicator of prostate cancer. Both PSA and human glandular kallikrein (hGK-1) are members of the kallikrein gene family and appear to be prostate-specific. The proposed studies will focus on the prostate-specific kallikrein genes, (prostate-specific antigen, PSA and human glandular kallikrein, hGK-1) to study androgen mediated gene regulation in the androgen responsive prostatic cell line, LNCaP, as a model system. Preliminary experiments have shown that LNCaP cells respond to androgens by increased production of both PSA and hGK-1. Sequence analysis of cloned 5' flanking regions of the kallikrein genes revealed a putative steroid response element (SRE). Therefore, PSA and hGk-1 specific DNA probes will be used to determine whether androgens act at the transcriptional and/or post-transcriptional level. Several complementary approaches will be used to characterize this putative SRE sequence and to identify other cis regulatory elements (i.e. prostate-specific elements) which are important for control of kallikrein gene expression. These will include: 1) gene transfer experiments, 2) in vitro DNA-protein interaction assays (e.g., DNase 1 foot printing, band shifting, methylation interference, etc.) and 3) mutational analysis. Achievement of these objectives should provide valuable insight into the androgenic and tissue-specific regulation of the prostatic kallikrein genes.

Source: https://www.industrydocuments.ucsf.edu/docs/fgbc0000